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Ventricular arrhythmia burst is an independent indicator of larger infarct size even in optimal reperfusion in STEMI

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Abstract

Objective: We hypothesized that ventricular arrhythmia (VA) bursts during reperfusion phase are a marker of larger infarct size despite optimal epicardial and microvascular perfusion.

Methods: 126 STEMI patients were studied with 24 h continuous, 12-lead Holter monitoring. Myocardial blush grade (MBG) was determined and VA bursts were identified against subject-specific background VA rates in core laboratories. Delayed-enhancement cardiovascular magnetic resonance imaging was used to determine infarct size.

Results: In the group with MBG 3 no significant differences were found for baseline characteristics between burst versus no burst (102 vs. 24). In those with optimal epicardial and microvascular reperfusion (TIMI 3, stable ST-recovery, and MBG 3), VA burst was associated with larger infarct size (N = 102/126; median 11.0 vs. 5.1%; p = 0.004).

Conclusion: In the event of MBG 3, VA bursts were associated with significantly larger infarct size even if optimal epicardial and microvascular reperfusion was present.

Keywords: Myocardial infarction; Ventricular arrhythmias; Magnetic resonance imaging; Microvascular obstruction

In the thrombolytic era, ventricular arrhythmias (VA) concomitant with ST segment normalization in ST elevation myocardial infarction (STEMI) were recognized as a sign of reperfusion [1]. These reperfusion arrhythmias typically consist of bursts of single or double ventricular premature beats (with long coupling intervals to the preceding normally conducted beats) and accelerated idioventricular rhythms. Their QRS configuration is consistent with an origin from the reperfused territory [1]. When primary PCI became available it was found that in complete epicardial recanalization with TIMI 3 flow, these bursts of ventricular reperfusion arrhythmias (VA bursts) were associated with larger infarct size and decreased left ventricular function [2].

Since the advent of coronary revascularization it was realized that just TIMI 3 flow was not sufficient to warrant optimal recovery at myocellular level. Phenomena such as distal embolization and damage at the microvascular level may interfere with recurrence of myocellular function. Therefore, although optimal epicardial recanalization (i.e. TIMI 3 flow) was present, it was found that infarct size also depended from more downstream existing markers, such as blush, microvascular obstruction (MVO) and ST segment recovery [3–7] Clinically, inadequate microvascular perfusion is independently associated with left ventricular remodeling and mortality [8]. Myocardial blush grade (MBG) is an angiographic classification to assess the microvascular integrity status after epicardial flow restoration (Fig. 1) and lower MBG is associated with larger infarct size, decreased left ventricular ejection fraction (LVEF), and increased mortality [9,10].

Abbreviations: DE-CMR, delayed enhancement cardiovascular magnetic resonance imaging; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MBG, myocardial blush grade; PCI, percutaneous coronary intervention; SPECT, Single-photon emission computed tomography; STEMI, ST elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; VA, ventricular arrhythmias; VPC, ventricular premature complex.

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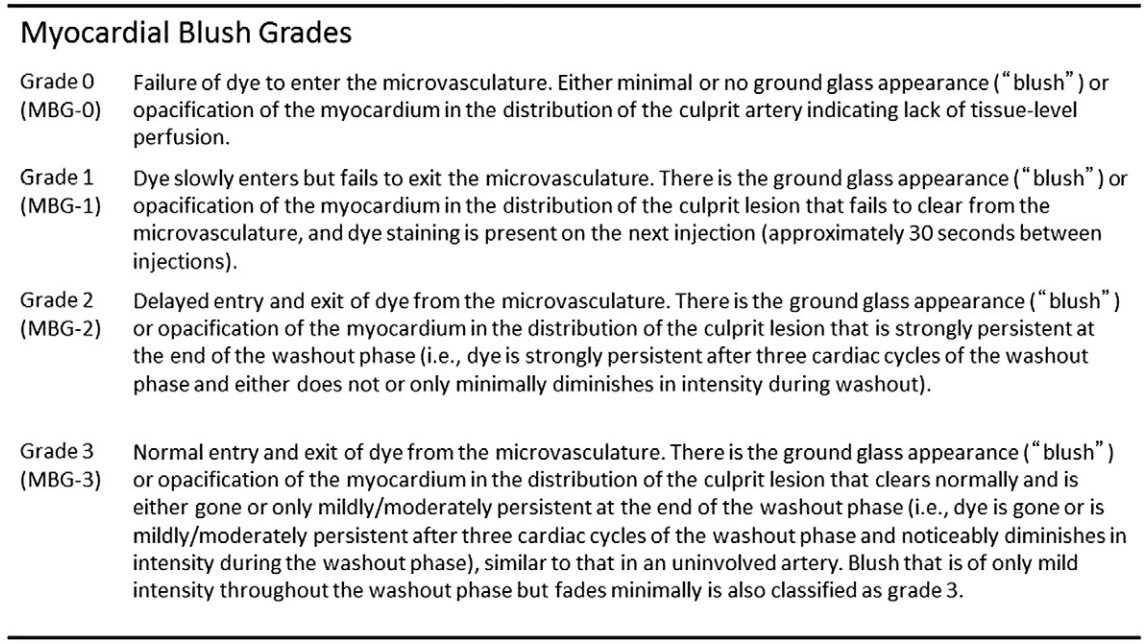

Fig. 1. Classification of myocardial blush grades.

The hypothesis of this study was, by exploring the relation between MBG, VA bursts and final infarct size measured by cardiac MRI, that even in patients with optimal epicardial and microvascular recanalization VAs indicate larger infarct size, identifying a more downstream, at the myocellular level existing, source of cell death in reperfused STEMI.

Methods

Study population

Patients included in the "proximal embolic protection study in patients undergoing primary angioplasty for acute myocardial infarction" (PREPARE) trial were used for the analyses. Since the Proxis™ proximal protection system used in the PREPARE trial did not influence final infarct size and LVEF [11], no distinction was made between the treatment and control group. Approval was granted by the Medical Ethical Committee of the Academic Medical Center (ISRCTN71104460) and written informed consent was obtained from all patients included. To study the ST-segment and ventricular arrhythmia behavior, 24-h holter recording starting before PCI was part of the study protocol.

The design of the PREPARE trial has been published earlier [11]. In brief, in the PREPARE trial, primary PCI was performed in patients with STEMI at the Academic Medical Centre in Amsterdam, The Netherlands, between December 2006 and June 2008. Inclusion criteria were: (1) age 18 years and above, (2) onset of symptoms of myocardial infarction less than six hours before presentation, (3) persistent ST-segment elevation of at least 2 mm in two or more contiguous leads on initial ECG, and (4) TIMI-graded flow 0 to 1 on diagnostic angiography. Exclusion criteria were: (1) any contraindication to the use of glycoprotein IIb/IIIa receptor antagonists, (2) a co-existent condition associated with a limited life expectancy, (3) prior coronary artery bypass grafting or administration of thrombolytic agents, (4) the presenting STEMI being a recurrence in the same myocardial area, and (5) proximal LAD occlusion causing inability for the PROXIS device to be used.

Exclusion criteria for ECG analysis were: (1) insufficient holter recording quality for determining presence or absence of VA burst either because of reperfusion before start of holter recording or excess noise, (2) previous MI, (3) inability to obtain cardiac magnetic resonance (CMR) recordings or inconclusive CMR recording for infarct size determination, (4) absence of successful epicardial flow restoration defined as TIMI flow ≤ 2, (5) inability to obtain stable ST recovery within 240 min, (6) late ST re-elevation, and (7) MBG ≤ 2.

Angiographic TIMI flow and blush grade assessment

At the end of each primary PCI, a final coronary angiogram was obtained. This post-procedural angiogram was used to assess TIMI flow, angiographic signs of distal embolization and the MBG by an independent observer at a corelab (Cordinamo, Wezep, The Netherlands). Epicardial coronary flow was assessed according the TIMI trial classification [12]. Angiographic distal embolization was defined as a filling defect, with an abrupt cut-off in the vessel located distally from the infarct-related coronary lesion. The assessment of myocardial blush grade was performed according to van 't Hof et al. [10] (Fig. 1).

ECG data acquisition

Continuous 12-lead ECG Holter recording (NEMON 180+, Northeast Monitoring, Maynard, MA, USA) was started immediately after admission and prior to the first angiogram. The NEMON system records a standard digital 12-lead ECG every 60 s in high-fidelity 720 Hz mode while

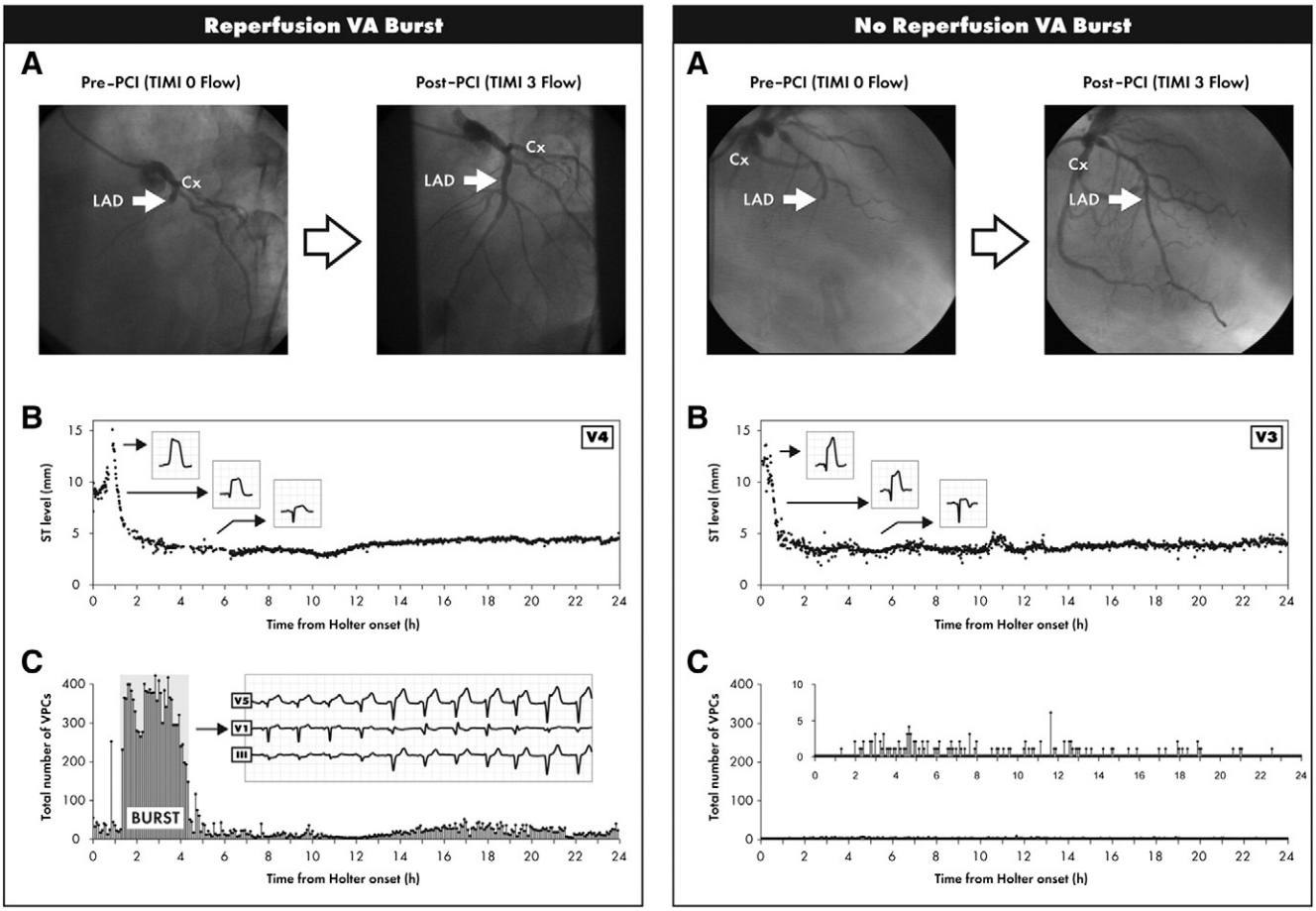

Fig. 2. Example of a patient with and a patient without VA burst. Concomitantly acquired coronary angiography assessments of pre- and post-primary percutaneous coronary intervention TIMI flow grades in two study subjects (1 A and 2 A) with a total occlusion in the proximal left anterior descending artery proximal (LAD); continuous digital 12-lead electrocardiography monitoring for ST-segment recovery analysis with both subjects having ≥50% stable ST-segment recovery (1B and 2B); and complete beat-to-beat Holter monitoring for quantitative rhythm analysis identifying (1C) or not identifying (2C) patient-specific ventricular arrhythmia 'bursts' by using independent statistical outlier detection methodology. Cx = circumflex artery; LMA = left marginal artery. (Majidi et al. Eur. Heart J 2009;30:757–764).

simultaneously archiving beat-to-beat Holter rhythm on a digital clock synchronized to the catheterization laboratory clock for accurate correlation of ECG changes, and holter rhythm changes. Continuous digital ECG and Holter data were encrypted and blinded to the clinical team and sent to the eECG core laboratory (eECG Core Laboratory, Maastricht University Medical Centre, Maastricht, The Netherlands) for independent blinded quantitative rhythm analysis.

Continuous ST recovery analysis

Method and criteria for continuous 12-lead ST-segment recovery analysis and reperfusion of the culprit lesion have been described in detail previously [6]. In short, peak ST-segment deviation is determined based on the lead with the greatest deviation taken from the most abnormal ECG recorded during monitoring. Steady state recovery was determined as >50% recovery from previous peak ST-segment levels in the most deviated lead, lasting >4 h without further ST-segment evolution (>100 uV) and patients were excluded from further analysis if time from last contrast injection to steady state was 240 min or more. Late ST elevation was diagnosed when recurrent ischemia following the first sustained 50% recovery (stable reperfusion) occurs with re-elevation of 150 uV, relative to the immediate previous recovery or baseline ST level in the most abnormal lead, occurring after stable reperfusion.

Quantitative rhythm analysis

For beat-to-beat quantitative rhythm analysis on all digital 3-lead holter recordings, holter 5 software (Northeast Monitoring, Maynard, MA, USA) was used [13]. All automatically assigned waveform labels were manually verified for each cardiac cycle from each subject to ensure accurate VA capture according to predefined criteria for ECG interpretation of VAs [13,14]. Fusion beats (normally conducted ventricular activation fused with ventricular premature complex (VPC) morphology) were also considered VPC's. To generate quantitative VA rates over a 24 h period, total VPC counts were bundled into 5 min blocks for temporal correlation with stable ST-segment recovery and angiographic observations (Fig. 2).

Defining VA burst

Quantitative VA rates over the course of Holter recordings were incorporated in a statistical outlier detection

Table 1
Patient characteristics.

	MBG 3				
	Burst not present (N = 24)		Burst present (N = 102)		P
Demographics					
age (years)	56.0	SD 8.5	57.8	SD 11.2	0.46
Male	23	95.8%	82	80.4%	0.08
Comorbidities					
BMI	27.2	SD 4.0	26.7	SD 3.8	0.60
Smoking current	14	58.3%	64	62.7%	0.80
Previous	5	20.8%	17	16.7%	
History of hypertension	6	25.0%	21	20.6%	0.59
Diabetes mellitus	2	8.3%	6	5.9%	0.65
Hypercholesteremia	3	12.5%	14	13.7%	1.00
Positive family history	7	29.2%	41	40.2%	0.36
Pre-existent AP	2	8.3%	3	2.9%	0.24
History of stroke	0	0.0%	2	2.0%	1.00
Peripheral artery disease	0	0.0%	2	2.0%	1.00
Medication					
β-blocker	3	12.5%	10	9.8%	0.71
acetyl salic acid	2	8.3%	9	8.8%	1.00
ADP-antagonist	0	0.0%	1	1.0%	1.00
Statin	4	16.7%	10	9.8%	0.47
Nitrates	0	0.0%	0	0.0%	
ACE-inhibitor	1	4.2%	4	3.9%	1.00
AT-II antagonist	2	8.3%	7	6.9%	0.68
Calcium-antagonist	4	16.7%	4	3.9%	0.04*
PCI					
Anterior MI	4	16.7%	27	26.5%	0.43
Multiple vessel disease	10	41.7%	30	29.4%	0.38
PCI of >1 lesion	0	0.0%	1	1.0%	1.00
Distal embolization	2	8.3%	11	10.8%	1.000
Duration of symptoms (min)[a]	173.0	SD 69.0	184.8	SD 91.5	0.57

ACE = angiotensin converting enzyme, ADP = adenosine diphosphate, AP = angina pectoris, AT = angiotensin, BMI = body mass index, CMR = cardiovascular magnetic resonance imaging, MBG = myocardial blush grade, MVO = microvascular obstruction, PCI = percutaneous coronary intervention.
* significant difference.
[a] duration of symptoms from onset till first balloon time.

method to automatically separate outliers of VA rates ('VA bursts'), from subject-specific background VA counts. Reperfusion VA bursts were identified as such if they occurred concomitantly with or subsequently to angiographic documentation of re-established TIMI 3 flow in the infarct related artery. Study subjects were dichotomously classified into the 'reperfusion VA burst' group or the 'no-VA burst' group based on having a significantly higher incidence of ventricular arrhythmias than background ventricular arrhythmias. This is illustrated in Fig. 2 panel 1C and 2C where over 24 h continuous ventricular activation is observed ("background arrhythmias"), but in panel 1C interrupted by a sudden increase in ventricular arrhythmias ("VA burst"), which was statistically identified using an outlier methodology as outlined in the supplement to this manuscript [13].

Cardiac Magnetic Resonance protocol

CMR examination was performed on a 1.5 T clinical scanner (Sonato/Avanto, Siemens, Erlangen, Germany), with the patient in a supine position, using a phased array cardiac receiver coil. ECG-gated cine images were acquired using a breath-hold segmented steady-state free precession sequence (echo time/repetition time of 1.2/3.2 ms; spatial resolution of 1.3 3 1.8 3 5 mm). Per patient short-axis views were obtained every 10 mm starting from base to apex and including the entire left ventricle. Late gadolinium enhancement images were obtained 10-15 min after the administration of a gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany; 0.2 mmol/kg) using a two-dimensional segmented inversion recovery gradient echopulse sequence (repetition time/echo time 9.6/4.4 ms, spatial resolution 1.6 3 1.3 3 5.0 mm), with slice position identical to the cine images. The inversion time was set to null the signal of viable myocardium and typically ranged from 250 to 300 ms. All data were analyzed using a dedicated software package (MASS 5.1) and by one experienced investigator who was blinded to the patient data. Left ventricular volumes were determined by planimetry of all short axis images in each patient and the left ventricular ejection fraction was calculated. The delayed gadolinium enhancement (DE)-CMR images and final infarct size were assessed described previously [15]. In brief, final infarct size was calculated by automatic summation of all slice volumes of hyper enhancement (signal intensity >6 SD above the mean signal intensity of remote myocardium).

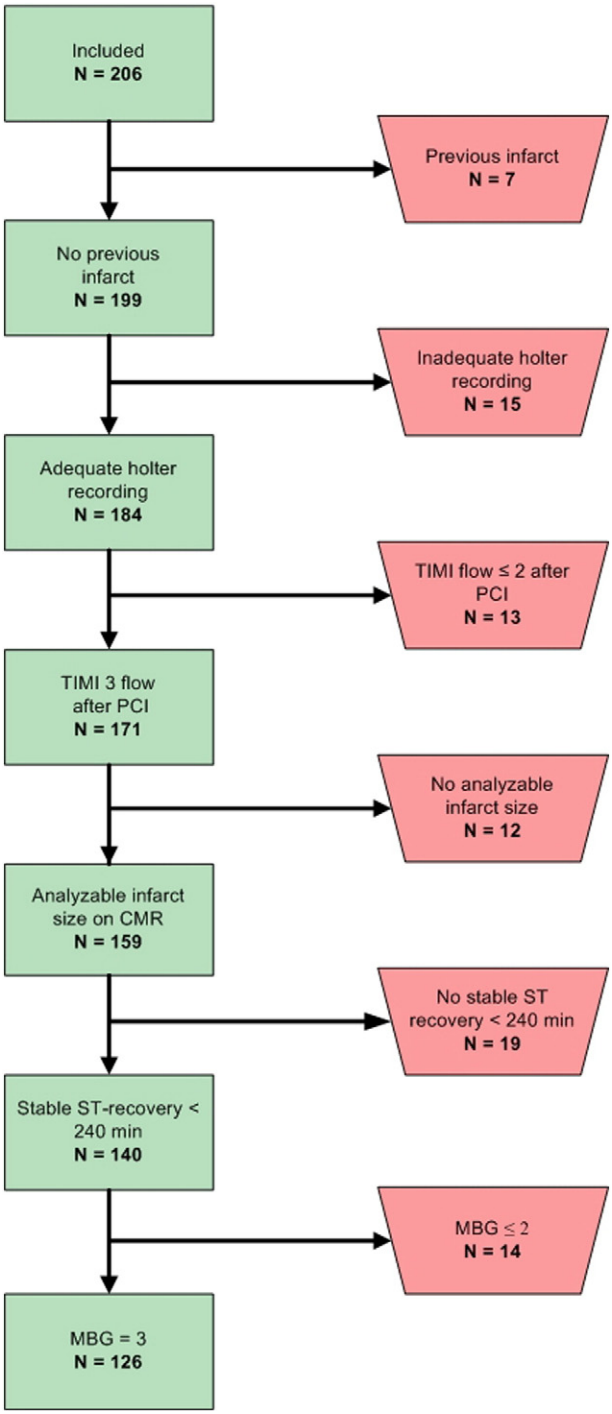

Fig. 3. Patient selection. Patient selection of combined dataset with reasons for exclusion.CMR = cardiac magnetic resonance, MBG = myocardial blush grade, PCI = percutaneous coronary intervention, TIMI = thrombolysis in myocardial infarction.

Statistical analysis

Univariable comparisons for patient characteristics and outcomes between patients with and patients without VA bursts were made using independent student t-test for parametric variables, Wilcoxon rank sum test for non-parametric variables, and Fisher exact test for dichotomous variables. The same was done in subgroup analysis of patients with blush 3 grade. A p value of <0.05 was considered statistically significant and all statistical tests were two-sided.

Multivariable linear regression analysis was performed to assess whether VA burst remained an independent predictor for infarct size and LVEF if corrected for covariates. The dependent variable was infarct size determined by DE-CMR. Covariates were selected by including known predictors for infarct size, displayed in Table 1, in the multivariate model and using the backwards stepwise model excluding those with p values >0.15. Covariates were added to a regression model starting with VA burst and presence or absence of blush grade 3. Data were analyzed using IBM SPSS statistics software version 19.

Results

The PREPARE study population consists of 206 patients, of whom 7 were excluded because of previous myocardial infarction, 15 patients had inadequate Holter recordings for VA burst determination, 13 patients did not obtain TIMI 3 flow after PCI, 12 were excluded because of insufficient CMR quality for infarct size determination, 19 had no stable ST recovery within 240 min or had late ST re-elevation, and 14 had MBG ≤ 2 (Fig. 3). The remaining 126 patients were used for analysis.

Table 1 shows patients characteristics according to the presence or absence of VA burst. The mean age was between 56 and 58 years in the respective groups and did not significantly differ. Most of the patients were male (80–96%) and VA burst occurred in 81.0% (102/126). No significant differences were found regarding baseline characteristics between the presence or absence of VA burst, except for the use of calcium antagonists. Patients who used a calcium antagonist before STEMI had on average a lower incidence of VA burst (4% vs 17%; $p = 0.04$). DE-CMR was performed within a median of 207 days (25%-75% quartiles; 135–365 days).

In case of optimal microvascular reperfusion (MBG 3), but with VA burst, infarct size doubled (11.0 vs. 5.1%; $p = 0.004$) compared to no VA burst (Fig. 4). Due to the relatively small infarcts in this study population LVEF was not significantly affected by the all or none presence of VA burst. In multivariable analysis the correlation between VA burst and infarct size remained significant ($B = 3.8$; $p = 0.04$) when correcting for other known predictors of infarct size, such as anterior wall location, age, and the use of β-blockers or ACE-inhibitors before the event (Table 2). In the multivariable analyses there was no significant effect of the use of calcium-antagonists before the event.

Discussion

This study shows that in the case of TIMI-3 flow and optimal microvascular reperfusion as indicated by TIMI-3 flow, stable ST-recovery and MBG 3, in patients with VA burst, infarct size was twice as large as those without VA burst.

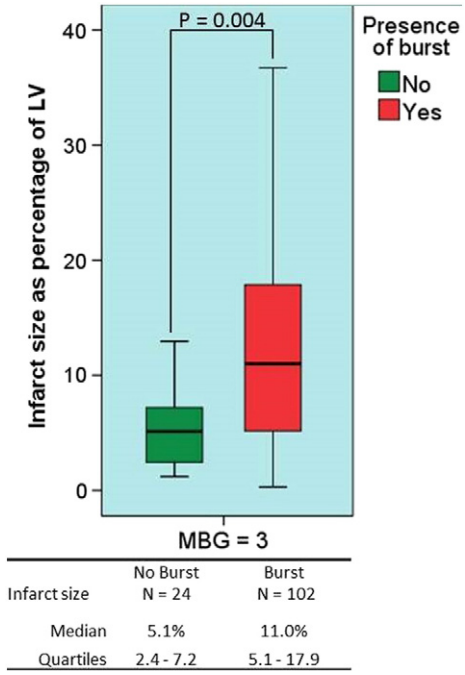

Fig. 4. Differences between VA burst present or absent. Box plots with corresponding medians and quartiles displaying the effect VA burst in the presence of optimal myocardial blush grade (MBG 3).

ST-segment resolution has been accepted as an important electrobiomarker for the success of reperfusion and infarct size after recanalization attempts in STEMI [6,7]. This study suggests that addition of the presence of VA burst further refines the prognostic model that identifies myocardial salvage and infarct size. VA burst has been shown to be a marker for larger infarct size, as measured by SPECT, in anterior wall STEMI [14,16]. Our results confirm previous findings using the more accurate measurement of DE-CMR [17]. Previous models of reperfusion VA burst depended on ^{99m}Tc-sestamibi SPECT to quantify the infarct size endpoint. SPECT is well validated in larger MI's, however is less reliable in smaller MI's with lower sensitivity for scintigraphic defects below 10 g of infarcted tissue [18]. DE-CMR, on the other hand, has superior spatial resolution and is superior in detecting smaller infarcts, such as subendocardial infarcts and infarcts in non-anterior locations [19,20]. Our results show that final infarct size is was in general relatively small, especially in non-anterior infarcts, in the setting of fast ST-recovery and optimal TIMI flow and blush grade. By using a more accurate method such as DE-CMR we could confirm results from a previous study that used SPECT, even in our population with small infarcts [16].

Until now it was not known whether VA bursts were markers either of suboptimal microvascular reperfusion, larger areas at risk or another pathophysiological mechanism such as reperfusion injury. This is the first study to describe that VA bursts indicate larger infarct size in the presence of not only optimal epicardial but also optimal (MBG determined) microvascular reperfusion directly after reperfusion by PCI using DE-CMR. There are nevertheless

Table 2
Multivariable analysis for final infarct size in patients with optimal blush grade.

	Coefficient	95% CI	P-value
Presence of VA burst	3.8	0.2 - 7.4	0.040
Anterior location	8.7	5.4 - 12.0	0.000
β-blocker use before event	−4.8	−9.5 - −0.1	0.045
ACE-inhibitor used before	7.7	0.4 - 15.0	0.039
Patient's age in years	0.1	−0.01 - 0.25	0.080
Constant	−8.9	−17.8 - −0.1	0.048

$R^2 = 0.27$.
ACE = angiotensin converting enzyme.

experimental reports showing a progression of microvascular obstruction (MVO) over the hours after reperfusion [21,22]. However CMR was performed after the (sub)acute phase and the difference in infarct size between the burst and no burst group remained. To exclude the involvement of suboptimal microvascular perfusion in the presence of VA burst and its correlation with infarct size, the hypothesis should also be tested in a population using MVO diagnosed by DE-CMR as a marker of impaired microvascular integrity. Moreover, the influence of the initial area at risk on the presence of VA burst should be tested to exclude an interaction for the outcome of infarct size. These questions are currently being studied by our group in ongoing research.

In the event of optimal epicardial reperfusion and optimal MBG, the occurrence of VA burst appeared a marker for larger infarct size. As such VA burst may be a potential useful biomarker for larger infarct size and worse outcome next to current markers of TIMI flow, stable ST recovery within 240 min, and myocardial blush grade. Such an additional biomarker could be useful in the early identification of patients at higher risk following recanalization attempts. "VA burst in our study was defined by a statistical outlier method, a burst of ventricular arrhythmias being differentiated from background arrhythmias using a 24 h holter recording. In clinical practice such a long recording time will likely not be needed as the occurrence of reperfusion arrhythmia burst can already be readily observed in the cath lab. However it is desirable to develop a robust algorithm enabling automatic assessment of "burst" or "no burst". Therefore, further research studying shorter observation times to quantify background arrhythmias should be done."

Limitations

One of the limitations of our study was a relatively small study population, yet, VA bursts were accurately assessed using continuous Holter monitoring and manual validation and infarct size was assessed using the current standard MRI. We did not have sufficient data regarding enzymatic infarct size because more than 50% of the population was referred back to the non-intervention hospitals in the region shortly after the recanalization procedure and enzymatic data from those hospitals was limited.

The number of patients with an anterior myocardial infarction was small in our study population. This is probably due to the exclusion of proximal LAD infarcts because of the inability to use the Proxis device in these laesions. Although the use of the Proxis device did not influence infarct size it did however exclude a part of the anterior infarctions.

We did not analyze the additional effect of medication given post myocardial infarction on final infarct size at the time of CMR. Because medication given after myocardial infarction is protocollized according to the ESC guidelines throughout the Netherlands we assume that it did not cause significant effect on infarct size between patients. However, we did not test this assumption.

For unknown reasons our study group showed a marked male preponderance. Therefore it is not certain whether the results can be transponed to a female population.

MBG as a marker for microvascular obstruction has some limitations and MVO on DE-CMR is currently being considered the preferred method. However, MBG directly after PCI is an intrinsically and early obtainable angiographic marker, while MVO on DE-CMR requires additional equipment and patient related suitability.

Conclusion

This is the first study to show that infarct size as measured by CMR is significantly larger in the occurrence of VA burst upon reperfusion in both anterior and non-anterior myocardial infarction, not only in the presence of optimal epicardial reperfusion but also when optimal microvascular reperfusion is present as defined by MBG 3. This suggests the cause of the larger damage to be localized at the myocellular level.

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Disclosures

The authors have no conflicts of interest to declare.

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